ABC of Methodology

This is a new Section of *Epidemiologia e Psichiatria Sociale*, that will regularly cover methodological aspects related to the design, conduct, reporting and interpretation of clinical and epidemiological studies. We hope that these articles will help develop a more critical attitude towards research findings published in the international literature and, additionally, will help promote the implementation of original research projects with higher standards in terms of design, conduct and reporting.

Corrado Barbui, *Section Editor* and Michele Tansella, *Editor* EPS

What is an intention to treat analysis?

ANDREA CIPRIANI and CORRADO BARBUI

Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Verona (Italy)

KEY WORDS: intention to treat, relative risk, randomisation, allocation concealment, statistics.

Randomization and allocation concealment are key methodological aspects in the design and conduct of comparative clinical trials (www.consort-statement.org). Random allocation generates treatment groups that are very similar in terms of known and unknown characteristics and, consequently, allows to reach correct conclusions about the true effect of an intervention under study. However, randomisation means little if investigators cannot include all randomly assigned participants in the primary analysis (Schulz & Grimes, 2002). Theoretically, statistical analyses should consider all patients according to their allocation as designated by the randomization procedure. This approach is called *intention-to-treat* analysis (ITT analysis). In the Figure it is reported the flow diagram of an hypothetical study that randomly allocated 100 patients per arm. At the end of the study period 39 (treatment A) and 46 responders (treatment B) were observed.

HOW CAN WE DESCRIBE THE EFFECT OF *TREATMENT A* OVER *TREATMENT B*?

If we carry out an ITT analysis, the risks to respond to treatment are 39/100 and 46/100 for treatment A and B, respectively. The relative risk (RR) (Cipriani *et al.*, 2007) is 0.85 (95% Confidence Interval [CI] 0.61 to 1.17). However, if we look at the reasons for not completing the study, we note that some participants did not receive any dose of the assigned treatment (1 and 3 participants for treatment A and B, respectively) or did not receive any post-baseline assessment even though they received at least one dose of study treatment (1 and 4, respectively). In some cases investigators believe that it is clinically more informative (and reasonable) to analyse data coming from participants who received at least one dose of treatment (the so called *on treatment* or *as-treated* analysis) or who received at least one post-baseline assessment. In this scenario, some patients are excluded from the analysis (and the analysis cannot be described as ITT). The RR is now slightly different (39/98 and 46/93, RR 0.80, 95% CI 0.59 to 1.11). Unfortunately, investigators often do not provide adequate information on the reason why some participants are excluded. It is difficult to interpret these missing data figuring out possible explanations. Participants drop out from trials or do not come back for assessment because they feel worse or because they feel better or because of many other reasons that may or may not be related with the treatment assigned by the randomization procedure. How to deal with such a potentially important uncertainty? In some cases investigators are interested in analysing responders as a proportion of the total number of patients who effectively completed the whole study (that is, patients who fully complied with the trial protocol – the so called, *per protocol* analysis). If we apply this scenario to our example, the RR changes dramatically and becomes statistically sig-

Address for correspondence: Dr. A. Cipriani, Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Piazzale L.A. Scuro 10, 37134 Verona (Italy).
Fax: +39-045-585.871
E-mail: andrea.cipriani@univr.it

nificant (39/71 and 46/63, RR 0.75, 95% CI 0.58 to 0.97). This example shows that the choice of the denominator does affect results.

BOTTOM LINE

In general, excluding subjects after randomisation undermines the comparability between treatments. The ITT approach provides the most convincing results because it prevents from biases associated with non-random loss of participants. It has been shown that the exclusion of some participants from the analysis can lead to misleading conclusions (Temple & Pledger, 1980). Consequently, for the primary analysis all patients who are randomly assigned should be analysed as part of the group to which they were initially assigned (Schulz & Grimes, 2002). Secondary analyses, that is analyses carried out to investigate secondary endpoints, can be carried out with different number of patients (i.e. different denominators) according to the aims of these analyses. In any case, if these analyses are not based on the total number of effectively randomised participants, they should be considered as a sort of "observational" evidence (Schulz & Grimes, 2002). Consistently, secondary analyses should be pre-planned and researchers should clearly label them as secondary and non-randomised comparisons. Sometimes published reports of studies do not specify these aspects and readers need to pay careful attention to denominators when reading and interpreting such results.

One big problem when interpreting study results is that the ITT approach is often inadequately applied and inadequately described (Hollis & Campbell, 1999). The wording "ITT analysis" may receive many different meanings and readers should have the possibility of clearly understanding how subjects deviating from the study protocol after random allocation, or subjects with missing responses, are handled by the study investigators in the statistical analysis. This is crucial to let readers critically assess the strengths and limitations of any statistical analyses. Many different ways of dealing with missing data have been described, and this topic will be covered in one of the next issues of EPS.

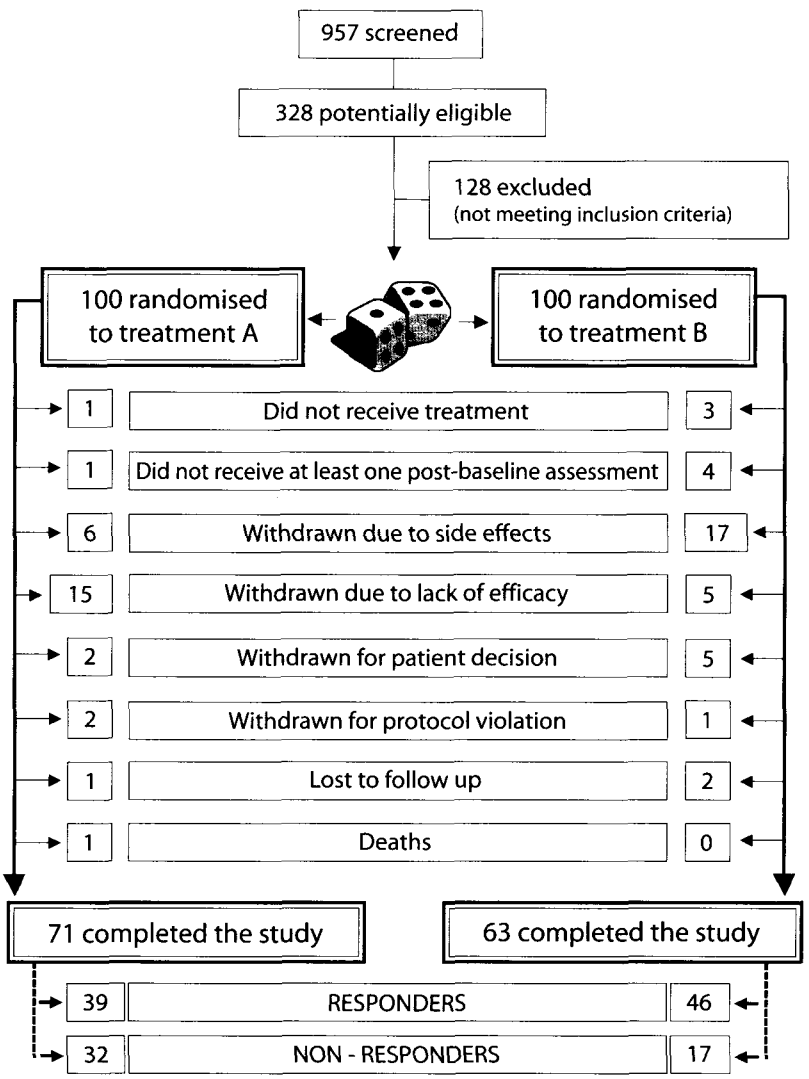
REFERENCES

Cipriani A., Nosè M. & Barbui C. (2007). What is a risk ratio? *Epidemiologia e Psichiatria Sociale* 16, 20-21.

Hollis S. & Campbell F. (1999). What is meant by intention to treat analysis? Survey of published randomised controlled trials. *British Medical Journal* 319, 670-674.

Schulz K.F. & Grimes D.A. (2002). Sample size slippages in randomised trials: exclusions and the lost and wayward. *Lancet* 359, 781–785.

Temple R. & Pledger G.W. (1980). The FDA's critique of the anturane reinfarction trial. *New England Journal of Medicine* 303, 1488-1492.



https://doi.org/10.1017/S1121189X00002645 Published online by Cambridge University Press